[197] Attorney Docket No. : ALX-152.1 CIP PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Evans et al.
Appl. No.	:	08/487,283
Filed	:	June 7, 1995
For	:	METHODS AND COMPOSITIONS FOR THE TREATMENT OF INFLAMMATORY DISEASES
Examiner	:	P. Gambel
Group	:	1644

Commissioner of Patents and Trademarks
Washington, D.C. 20231

SUPPLEMENTAL RESPONSE

Dr. Scott Rollins, Attorney Mark Farber, and the undersigned attorney would like to thank Examiner Gambel for the helpful interview conducted at the Patent and Trademark Office on June 27, 2000.

At the interview, the following references were discussed and the distinctions set forth below were pointed out to the Examiner:

I. **BIESECKER et al., "The release of C5a in complement-activated serum does not require C6" J Immunol 143:1228-1232, 1989.**

Biesecker et al. is not enabling with regard to an antibody which exhibits specific binding "targeted to the alpha chain of human complement component C5," as claimed by applicants, since the reference does not

disclose whether its anti-C5b monoclonal antibody, i.e., the A3-27 antibody, binds to the α or β chain of human C5.[1]

II. **GICLAS et al., "Preparation and characterization of monoclonal antibodies against the fifth component of rabbit complement (C5)" J Immunol Methods 105:201-209, 1987.**

Giclas et al. is not enabling with regard to an antibody which exhibits specific binding "targeted to the alpha chain of human complement component C5," as claimed by applicants, since the reference does not disclose whether its anti-C5 monoclonal antibodies bind to the α or β chain of human C5 (see note 1 above).

III. **HUGO et al., "Monoclonal antibodies against neoantigens of the terminal C5b-9 complex of human complement" Biosci Rep 5:649-658, 1985.**

Hugo et al. is not enabling with regard to an antibody which exhibits specific binding "targeted to the alpha chain of human complement component C5," or an antibody which "does not specifically bind to the human complement activation product free C5a," as claimed by applicants, since the reference (1) does not disclose whether its anti-C5 monoclonal antibody, i.e., the 1E8 antibody, binds to the α or β chain of human C5 (see

[1] Each of applicants' independent Claims 1, 27, and 31 calls for an antibody that exhibits specific binding "targeted to the alpha chain of human complement component C5." The antibodies of Claims 26 and 30 have this property, as does the hybridoma of Claim 29 through its production of the antibody of Claim 30.

note 1 above) and (2) does not disclose the binding characteristics of that monoclonal antibody to human free C5a.[2]

IV. **KLOS et al., "Detection of native human complement components C3 and C5 and their primary activation peptides C3a and C5a (anaphylatoxic peptides) by ELISAs with monoclonal antibodies" J Immunol Methods 111:241-252, 1988.**

The 568 anti-C5 monoclonal antibody of this reference binds to the β chain of human C5, while the 557 and 561 antibodies bind to human free C5a. Applicants' claims call for an antibody that (1) exhibits specific binding "targeted to the alpha chain of human complement component C5" (see note 1 above) and (2) "does not specifically bind to human complement activation product free C5a" (see note 2).

V. **MOLLNES et al., "Identification of a human C5 beta-chain epitope exposed in the native complement component but concealed in the SC5b-9 complex" Scand J Immunol 28: 307-312, 1988.**

The anti-C5 monoclonal antibody which is the main subject of this reference, i.e., the 568 antibody, binds to the β chain of human C5. Applicants' claims call for an antibody that exhibits specific binding "targeted to the alpha chain of human complement component C5" (see note 1 above).

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[2] Each of applicants' independent Claims 1, 27, and 31 calls for an antibody that "does not specifically bind to the human complement activation product free C5a." The antibodies of Claims 26 and 30 have this property, as does the hybridoma of Claim 29 through its production of the antibody of Claim 30.

The remaining anti-C5 monoclonal antibodies of the reference, i.e., i.e., the 555, 556, 558, 559, 564, 569, and 572 antibodies, are not enabling with regard to an antibody which exhibits specific binding "targeted to the alpha chain of human complement component C5" or an antibody which "does not specifically bind to the human complement activation product free C5a," as claimed by applicants, since the reference does not disclose whether these antibodies bind to the α or β chain of human C5 and also does not disclose the binding characteristics of these antibodies to human free C5a (see notes 1 and 2 above).

VI. MOONGKARNDI et al., "Immunological and functional properties of two monoclonal antibodies against human C5" Immunobiol 165:323, 1983.

Moongkarndi et al. is not enabling with regard to an antibody which exhibits specific binding "targeted to the alpha chain of human complement component C5," or an antibody which "does not specifically bind to the human complement activation product free C5a," as claimed by applicants, since the reference does not disclose whether its anti-C5 monoclonal antibodies bind to the α or β chain of human C5 and also does not disclose the binding characteristics of those monoclonal antibodies to human free C5a (see notes 1 and 2 above).

VII. REED et al., "Synthesis of complement component C5 by human B and T lymphoblastoid cell lines" Immunogenetics 31:145-151, 1990.

Reed et al. is not enabling with regard to an antibody which exhibits specific binding "targeted to the alpha chain of human complement component C5," or an antibody which "does not specifically bind to the human complement activation product free C5a," as claimed by applicants, since the reference does not disclose whether its anti-C5 monoclonal antibodies bind to the α or β chain of human C5 and also does not disclose the binding characteristics of those monoclonal antibodies to human free C5a (see notes 1 and 2 above).

VIII. ROTTINI et al., "Monoclonal antibodies as probes to investigate the molecular changes of C5 associated with the different stability of the molecule on sheep erythrocytes and Escherichia coli 0111:B4" J Immunol 146:643-647, 1991.

Rottini et al. is not enabling with regard to an antibody that "does not specifically bind to the human complement activation product free C5a," as claimed by applicants, since the reference does not disclose the binding characteristics of its anti-C5 monoclonal antibodies to human free C5a (see note 2 above).

IX. SUNDSMO, "Leukocyte complement: a possible role for C5 in lymphocyte stimulation" J Immunol 131:886-891, 1983.

Sundsmo is not enabling with regard to an antibody which exhibits specific binding "targeted to the alpha chain of human complement

component C5," or an antibody which "does not specifically bind to the human complement activation product free C5a," as claimed by applicants, since the reference does not disclose whether its anti-C5 monoclonal antibodies bind to the α or β chain of human C5 and also does not disclose the binding characteristics of those monoclonal antibodies to human free C5a (see notes 1 and 2 above).

X. WURZNER et al., "Inhibition of terminal complement complex formation and cell lysis by monoclonal antibodies" Complement Inflamm 8:328-340, 1991.

The anti-C5 monoclonal antibodies of this reference, i.e., the N19-8 and N20-9 antibodies, bind to the β chain of C5. Applicants' claims call for an antibody that exhibits specific binding "targeted to the alpha chain of human complement component C5" (see note 1 above).

In addition to discussing the above references, the clinical efficacy of applicants' antibodies was discussed with the Examiner and reference was made to published reports regarding that efficacy. Attached hereto as Exhibit A are the following references relating to applicants' clinical results: Fitch et al., Circulation, 1999, 100:2499-2506; Rollins, S., Immuno-pharmacology, 2000, 49:69; Jain et al., Arthritis & Rheumatism, 1999, 42:S77; and Rollins et al., Molecular Immunology, 1998, 35:397.

As discussed therein, applicants' antibodies have been found to reduce heart and brain tissue damage resulting from cardiopulmonary

bypass procedures and to exhibit anti-inflammatory activity in arthritis and cardiopulmonary bypass patients. Such efficacy is plainly not disclosed or suggested by the references of record in this application, whether those references are taken alone or in combination.

In view of the foregoing, applicants believe that each of their Claims 1-8, 18-23, 25-27, and 29-31 (the Group I claims) is properly patentable. Allowance of the application is thus respectfully requested.

Respectfully submitted,

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